A somitic Wnt16/Notch pathway specifies haematopoietic stem cells.

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Public Summary:
Hematopoietic stem cells are an important population of cells that continuously produce and replace red blood and immune system cells during life. These rare cells are the important element of bone marrow transplants, which are used to treat a variety of conditions including many forms of blood cancer. Understanding how hematopoietic stem cells are made during embryonic development is important because it could teach us how to make such cells in the laboratory, and possibly allow circumvention of donor immune compatibility issues. In this research we describe a previously unknown set of molecular inputs that are required to make hematopoietic stem cells during embryonic development. Eventually these findings may help us discover the complete set of molecular controls necessary for making hematopoietic stem cells.

Scientific Abstract:
Haematopoietic stem cells (HSCs) are a self-renewing population of cells that continuously replenish all blood and immune cells during the lifetime of an individual. HSCs are used clinically to treat a wide array of diseases, including acute leukaemias and congenital blood disorders, but obtaining suitable numbers of cells and finding immune-compatible donors remain serious problems. These difficulties have led to an interest in the conversion of embryonic stem cells or induced pluripotent stem cells into HSCs, which is not possible using current methodologies. To accomplish this goal, it is critical to understand the native mechanisms involved in the specification of HSCs during embryonic development. Here we demonstrate in zebrafish that Wnt16 controls a novel genetic regulatory network required for HSC specification. Non-canonical signalling by Wnt16 is required for somitic expression of the Notch ligands deltaC (dlc) and deltaD (dld), and these ligands are, in turn, required for the establishment of definitive haematopoiesis. Notch signalling downstream of Dlc and Dld is earlier than, and distinct from, known cell-autonomous requirements for Notch, strongly suggesting that novel Notch-dependent relay signal(s) induce the first HSCs in parallel to other established pathways. Our results demonstrate that somite-specific gene expression is required for the production of haemogenic endothelium.